REMARKS

I. Status of the Claims

Claims 1-12, 14 and 15 are pending and stand rejected under 35 U.S.C. §112, second paragraph and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Applicants have provided a substantially revised claim set that almost exclusively provides clarifying amendments to the existing claims. Support for the amendment to claims 8 and 10 can be found at paragraph [0014] of the specification.

II. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-12, 14 and 15 are rejected as indefinite under the second paragraph of §112. First, claims 1 and 10-12 are said to be indefinite because it is said not to be clear how the various ligands "relate to the diagnosis of vascular dysfunction or disease." However, intended uses are irrelevant to the patentability of an article of manufacture, such as a kit. Also, the language relating to vascular dysfunction or disease has been removed from the claims. Thus, the claim is definite.

Second, claims 1 and 14 are said to be indefinite in that it is said to not be clear what is being detected. Claim 14 has been canceled. With respect to claim 1, again, intended uses are irrelevant to the patentability of an article of manufacture. Moreover, the claim has been clarified to contain two reagents, the second of which is used to detect "antibodies bound to phosphocholine." Thus, the claim is believed to be clear.

Third, claim 2 is said to be indefinite as requiring a correlation step. Once again, intended uses are irrelevant to the patentability of an article of manufacture. Also, the language

relating to vascular dysfunction or disease has been removed from the claims. Thus, the claim is believed to be definite as written.

Reconsideration and withdrawal of the rejections is therefore respectfully requested.

III. Rejections Under 35 U.S.C. §103

A. Barquinero, Baldo and Foster

Claims 1, 5-7, 12 and 14 stand rejected as obvious over Barquinero *et al.*, in view of Baldo *et al.* and Foster *et al.* Barquinero is cited as teaching correlation between SLE and anti-PAF levels (with SLE allegedly leading to inflammation and cardiovascular disease), Baldo is cited for phospholipid analogs that are sufficient to induce anti-PAF antibodies, PAF being known to be insufficiently antigenic to produce anti-PAF antibodies in standard immunization schemes, and Foster is cited as teaching kits. Applicants traverse.

1. Interview

Applicants wish to thank the examiner and her supervisor for the courtesy of an in-person interview, held at the Patent and Trademark Office, on November 15, 2006, including Examiner Cook, SPE Long Le, and the undersigned. During the interview, the undersigned addressed the Barquinero and Baldo references cited above and explained why the examiner had either misinterpreted the substance of the teachings of those papers, or improperly attributed motivation to make modifications to the art where none existed. While agreement was not reached, it was agreed that Barquinero did not teach correlation between anti-PAF and autoimmune disease, *e.g.*, SLE, as previously argued. It was agreed that applicants would reiterate their position with regard to all of the references and non-obviousness in a formal response to the action. ***As urged at the conclusion of the interview, applicants request that should the examiner fail to find the***

claims as submitted herein allowable, a telephone call to the undersigned be initiated prior to issuance of a further action.

2. Lack of a Prima Facie Case

First, applicants would like to draw the examiner's attention to new claim 1, which now reads as follows:

> A kit comprising:
>
> (a) phosphocholine; and
> (b) a reagent for detecting antibodies bound to phosphocholine.

As discussed above, the examiner cited Barquinero as teaching a correlation between anti-PAF antibodies and autoimmune diseases such as SLE, with SLE having inflammatory and hence cardiovascular disease components. As applicants' representative pointed out during the interview, however, Barquinero does ***not*** teach a correlation with anti-PAF antibodies and autoimmune disease. Much to the contrary, Barquinero readily admits that "[o]nly differences between syphilis and normal blood donors were significant ($P < 0.01$)." Barquinero, Discussion, 1st para. Indeed, of some 128 SLE patients and 28 PAPS patients, only 10 and 5 patients, respectively, showed elevated anti-PAF, as opposed to 30 out of 40 syphilis patients. Barquinero, Table 1. During the interview, the examiner and her supervisor agreed that Barquinero could not provide a link between anti-PAF and early CVD. However, it might be argued that Barquinero does, in fact, provide a link between anti-PAF antibodies and syphilis, and hence a motivation to look for anti-PAF antibodies.

Nonetheless, applicants believe the rejection to be fatally flawed. The citation of the secondary reference, Baldo, is illogical in the context of an immunoassay. Taking the examiner's

assertions regarding Baldo at face value, one interested in ***generating*** anti-PAF antibodies might be motivated to use various of Baldo's phospholipids due to the apparent low antigenicity of PAF. However, when the goal is to ***identify*** anti-PAF antibodies, there would be ***no*** logical reason to use something other than ***PAF itself***. PAF is not in short supply, expensive, or difficult to use. Moreover, as noted by Barquinero, there is a difference in the ability of charged phospholipids to ***cross-react*** with anti-PAF, and in their ability to ***compete*** with PAF for anti-PAF binding. Indeed, the Muzya reference (cited below) comments that "[i]n contrast to highly specific antibodies to PAF, aPC antibodies are not highly specific and reactive with other phospholipids." Muzya, 2nd para. following Table 2[1]. This is a clear condemnation of using anything other than PAF in anti-PAF assays. Finally, Foster is merely cited for disclosure of kit configurations, and says nothing about PAF analogs, and cannot remedy this defect.

Thus, in sum, there is no motivation for using anything other than PAF in an assay for anti-PAF. Thus, the combination of Baldo with Barquinero and Foster is improper, and for this reason alone, the rejection must fall. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. Barquinero, Baldo, Foster and Ostermann

Claims 2-4, 8-10 and 15 are rejected over Barquinero, Baldo and Ostermann *et al.* The first three references are cited as above, while Ostermann is cited as teaching PAF quantification in serum and plasma as well as correlation/diagnosis with atherosclerosis, alleged to be a cardiovascular disease (CVD). In the revised claims presented above, indeed, claim 2 (but no other) recites reagents for detecting cholesterol, blood lipids or p-hydroxyphenylaldehyde-lysine,

[1] Applicants are providing a certified translation of the entire Muzya *et al.* paper, as the examiner had (and apparently has) only access to a translated abstract.

and applicants submit that this claim clearly implicates testing for the purpose of diagnosing early CVD. Thus, to the extent the present rejection is applied to this claim, it is traversed.

As stated above, Barquinero cannot provide any relevant teaching with regard to CVD, a point which both the examiner and her SPE acknowledged during the interview. In addition, Baldo is silent on this point. Hence, the examiner has turned to Ostermann for such a teaching. Ostermann cannot provide that link, however, for the simply reason that ***it never once mentions anti-PAF antibodies***. What Ostermann does appear to teach is a correlation between the activity of a PAF acetylhydrolase activity and atherosclerosis. However, Ostermann never shows that PAF degradation correlates with a reduced level of PAF, and even more importantly, it never addresses anti-PAF antibodies (much less anti-PC antibodies) that might actually be expected to ***drop*** if indeed the PAF levels in these patients are reduced.

Thus, it is submitted that the rejection here still is flawed for the reason given above – that Baldo does not provide sufficient motivation to use PAF analogs in an anti-PAF binding ***assay***. Moreover, because none of the cited references, including Ostermann, teach a correlation of anti-PAF antibodies with CVD, the rejection fails for this second reason. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

C. Barquinero, Baldo, Foster and Muzya

Claim 11 is rejected over Barquinero, Baldo and Foster, as cited above, and further in view of Muzya. Muzya is being cited as providing motivation to use phosphocholine as a ligand to detect antibodies to PAF, albeit in the context of gynecologic disorders (as opposed to CVD or syphilis). Though claim 11 has been canceled, applicants wish to address the substance of the rejection as it may pertain to other pending claims. In that regard, applicants again traverse the rejection.

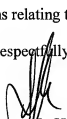
As noted above, Muzya itself comments on the difficulties associated with examining anti-phosphocholine antibodies. "In contrast to highly specific antibodies to PAF, aPC antibodies are not highly specific and reactive with other phospholipids." Muzya, 2nd para. following Table 2. This is a clear condemnation of using anything other than PAF in anti-PAF assays. Barquinero too suggests differences between PAF and other phospholipids when it comes to cross-reactivity *versus* competition, further supporting the notion that one would use PAF, and not an analog, in a binding assay for anti-PAF antibodies. And as discussed above, the other cite references cannot remedy this defect.

Thus, again, there is no motivation for using anything other than PAF in an assay for anti-PAF antibodies, and the additional combination of Muzya with Barquinero, Baldo and Foster is improper for the reasons given above. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should there be any questions regarding this submission a telephone call to the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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